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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,088	10/02/2001	Edwin C. Gravereaux	71417/55062	9526

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EXAMINER	
HUNNICUTT, RACHEL KAPUST	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,088	GRAVEREAUX ET AL.	
	Examiner	Art Unit	
	Rachel K. Hunnicutt	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7-26 and 28-82* is/are pending in the application.

4a) Of the above claim(s) *10-21,31-41 and 74-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7-9,22-26,28-30,42-73,81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

Applicant's amendment filed October 20, 2004 is acknowledged. Claims 10-21 and 31-41 are withdrawn as being drawn to a non-elected invention. Claims 2, 4-6, and 27 have been canceled. Claims 1, 3, 7, 9, 23-26, 29, 42, and 43 are amended. Claims 47-82 are new. Claims 74-80 are withdrawn from consideration as being drawn to a non-elected invention. The current claims are drawn to methods of administering VEGF-2 polypeptides classified in class 514, subclass 2. Claims 74-80 are drawn to administering nucleic acid sequences encoding VEGF-2 polypeptides, *i.e.* gene therapy, which is classified in class 514, subclass 44.

Claims 1, 3, 7-9, 22-26, 28-30, 42-73, and 81-82 are under consideration. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

The objection to the specification for containing embedded hyperlinks is withdrawn in response to Applicant's amendments to the specification.

The objection to the specification regarding the use of trademarks is withdrawn in response to Applicant's amendments to the specification.

The objection to claim 4 as being in improper form is withdrawn in response to Applicants' cancellation of the claim.

The objection to claim 6 for containing a typographical error is withdrawn in response to Applicants' cancellation of the claim.

The objection to claim 29 for containing a typographical error is withdrawn in response to Applicants' amendment to the claim.

The rejection of claims 3, 9, 23-25, 28, and 42-43 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn in response to Applicants' amendment to the claims. The claims are now drawn to administering VEGF-2 polypeptides. The rejection of claims 2, 4-6, and 27 under 35 U.S.C. 112, first paragraph, for lack of enablement, is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 3, 9, 23-25, 28, and 42-43 under 35 U.S.C. 112, first paragraph, as not complying with the written description requirement, is withdrawn in response to Applicants' amendment to the claims. The claims are now drawn to administering VEGF-2 polypeptides. The rejection of claims 2, 4-6, and 27 under 35 U.S.C. 112, first paragraph, as not complying with the written description requirement, is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1, 3, 7-8, 26, 29-30, and 45-46 under 35 U.S.C. 102(e) as being anticipated by Achen *et al.* is withdrawn in response to Applicants' amendment to the claims. Achen *et al.* do no anticipate a method of administering VEGF-2. The rejection of claims 2 and 5-6 under 35 U.S.C. 1-2(e) as being anticipated by Achen *et al.* is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1, 3, 7-8, 22, 25-26, 29-30, 42, and 45-46 under 35 U.S.C. 102(e) as being anticipated by Alitalo *et al.* is withdrawn in response to Applicants' amendment to the claims. The rejection may be reinstated, however, should Applicants cancel the limitation that the administration be repeated at least twice in response to the new matter rejection listed below. The rejection of claims 2, 4-6, and 27 under 35 U.S.C. 102(e) as being anticipated by Alitalo *et al.* is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1, 3, 9, 29-30, and 42-43 under 35 U.S.C. 102(a) as being anticipated by Eicher is withdrawn in response to Applicants' amendment to the claims. The rejection may be reinstated, however, should Applicants cancel the limitation that the administration be repeated at least twice in response to the new matter rejection listed below.

The rejection of claims 2 and 4-6 under 35 U.S.C. 102(a) as being anticipated by Eicher is withdrawn in response to Applicants' cancellation of these claims.

The rejection of claims 1, 3, 7-8, 22, 25-26, 29-30, 42, and 45-46 under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hu *et al.* is withdrawn in response to Applicants' amendment to the claims. The rejection may be reinstated, however, should Applicants cancel the limitation that the administration be repeated at least twice in response to the new matter rejection listed below. The rejection of claims 2, 4-6, and 27 under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hu *et al.* is withdrawn in response to Applicants' cancellation of these claims.

Claim Rejections/Objections Maintained/New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 is dependent on canceled claim 4. The scope of claim 42 cannot be determined.

The rejection of claims 1, 7-8, 22, 26, 29-30, and 44-46 under 35 U.S.C. 112, first paragraph, as not being enabled for a method of inducing formation of new lymphatic vessels by administering fragments of VEGF-2, is maintained for reasons of record on p. 4-5 of paper no. 0504 and is applied to new claims 47-48, 52-57, 59-63, 65-73, and 81-82.

Applicants argue that no undue experimentation is required by the definition of "effective fragment" on p. 17, lines 1-4, because "the specification also provides assay methods, which can be used to measure activity of VEGF-2 variants" (p. 26 of the response). Applicants argue that one of ordinary skill in the art would know how to make and use the claimed invention in view of the teachings of the specification and that many fragments are known in the art.

Applicants' arguments have been fully considered but have not been found to be persuasive. The claims are drawn to methods for inducing the formation of new lymphatic vessels by administering fragments of VEGF-2. However, Applicants have provided no guidance as to what size fragment would be sufficient or what region of VEGF-2 would be effective for achieving the formation of new lymphatic vessels. Applicants define an "effective fragment" as an "amino acid sequence that exhibits at least about 70%, preferably at least about 80% to about 95% of the lymph vessel promoting activity of the corresponding full-length protein" (see p. 17, lines 1-4 of the specification). Certain positions in a protein sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. One of skill in the art would not know which amino acids may be deleted from VEGF-2 in order to yield effective fragments of VEGF-2. For example, Joukov *et al.* teach that several VEGF-2 fragments which have increased activity towards VEGFR-3, but only the fully process VEGF-2 could activate VEGFR-2 (1997, *The EMBO Journal* 16(13): 3898-3911, see p. 3902-3905). Thus, as stated in the previous office action, depending on the sequence of the VEGF-2 fragment, the fragment may not be effective in inducing the formation of new lymphatic vessels.

Due to the large quantity of experimentation necessary to generate the fragments recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on polypeptide structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

The rejection of claims 1, 7-8, 22, 26, 29-30, and 44-46 under 35 U.S.C. 112, first paragraph, as not complying with the written description requirement, is maintained for reasons of record on p. 5-7 of paper no. 0504 and is applied to new claims 47-48, 52-57, 59-63, 65-73, and 81-82.

Applicants argue that the specification provides assay methods which can be sued to measure the activity of VEGF-2 variants, and more particular fragments are claimed and a way of testing is provided (p. 28 of response).

Applicants' arguments have been fully considered but have not been found to be persuasive. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. The instant disclosure of a single species of protein, VEGF-2, does not adequately describe the scope of the claimed genus, which encompasses hundreds of different peptides with varying structures and functions. The instant specification fails to provide sufficient descriptive information, such as regions of VEGF-2 which are critical to inducing formation of lymphatic vessels. Applicants are claiming a species which has not been sufficiently described, *i.e.* Applicants are claiming sequences of VEGF-2 that have not yet been identified. Only once the VEGF-2 fragments have been generated and their functions have been determined can a person of skill in the art determine that the VEGF-2 fragments are able to induce formation of lymphatic vessels. Thus, no identifying characteristics or properties of the instant VEGF-2 fragments are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, one of skill in the art would doubt that Applicants had possession of the claimed species at the time the application was filed.

Claims 1, 3, 7-9, 22-26, 28-30, 42-56, and 62-73 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 3, 7-9, 22-26, 28-30, and 42-56 encompass methods for inducing formation of new lymphatic vessels wherein VEGF-2 or an effective fragment thereof is administered, and then the administration is repeated at least twice. However, nowhere in the specification is there

any mention of administering VEGF-2 polypeptides, and then repeating the administration at least twice. In Example 4, Applicants teach repeating the injection of DNA three times, and on p. 30 Applicants teach administering 8 injections of DNA, but neither of these examples refer to administering the VEGF-2 polypeptide and then repeating the administration at least twice. Claims 47 and 48 encompass methods wherein "the administration is repeated over a period of about two weeks." Again, nowhere in the specification is there any mention of repeating the administration of VEGF-2 polypeptides over a period of two weeks. There is no written support for the claimed methods. Such methods are considered to be new matter.

Claims 62-73 encompass methods for inducing formation of new lymphatic vessels wherein VEGF-2 polypeptides are administered topically. Claims 66-72 refer to the gels or gelling agents comprising an effective amount of the VEGF-2 polypeptide. The specification is silent as to topically administering VEGF-2 polypeptides. On p. 30 the specification refers to the topical administration of nucleic acid molecules, but it does not refer to topically applying compositions comprising polypeptides. There is no written support for topically applying polypeptides or applying gels comprising polypeptides. Such methods are considered to be new matter.

Claim Rejections - 35 USC § 102

Claim 82 is rejected under 35 U.S.C. 102(e) as being anticipated by Alitalo *et al.* (U.S. Patent No. 6,730,658, cited in paper no. 0504). New claim 82 is drawn to a method for inducing formation of new lymphatic vessels in a mammal by administering VEGF-2, wherein the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with same, and the VEGF-2 is administered to the mammal before exposing the mammal to conditions conducive to damaging lymphatic vessels. Alitalo *et al.* teach administering VEGF-C (also known in the art as VEGF-2) to patients that are in need of lymphatic tissue growth (column 49, lines 43-49). Alitalo *et al.* teach the use of VEGF-C polypeptides and effective fragments thereof for the treatment of the physical loss of lymphatic vessels and lymphatic vessel occlusion (column 5, lines 25-30 and column 9, lines 46-57). Alitalo *et al.* teach that VEGF-C can be used "to treat or prevent inflammation, edema, aplasia of

the lymphatic vessels, lymphatic obstruction, elephantiasis, and Milroy's disease" (column 9, lines 4-7). Preventing inflammation or edema implies that the VEGF-C is administered prior to a condition which would lead to inflammation or edema, thus claim 82 is anticipated by Alitalo *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 7, 8, 26, 29, 30, 42, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alitalo *et al.* as discussed above. Claims 1, 3, 7, 8, 26, 29, 30, 42, 45, and 46 have the limitation that VEGF-2 is administered at least twice in order to induce formation of

new lymphatic vessels. Alitalo *et al.* teach administering VEGF-2 in order to induce formation of new lymphatic vessels, however Alitalo *et al.* do not teach administering VEGF-2 at least twice. It would have been obvious to one skilled in the art to repeat the administration of VEGF-2 if the first dose were insufficient to induce the formation of new lymphatic vessels. Optimization of conditions through routine experimentation is not considered to be an advancement of the useful arts. MPEP 2144. See *In re Hoeschele*, 406 F. 2d 1403, 160 USPQ 809 (CCPA 1969) ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."). The skilled artisan would have expected the modified method to be equally effective in inducing the formation of new lymphatic vessels.

Claims 1, 3, 9, 29, 30, 42, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eicher (WO 99/49882, cited in the previous office action). Claims 1, 3, 29, 30, and 42 are as stated above. Claims 9 and 43 have the added limitation that the VEGF-2 be co-administered with at least one angiogenic protein. Eicher teaches the administration of VEGF and VEGF-2 to promote new blood and lymphatic vessel formation (see p. 4), and Eicher teaches that VEGF and VEGF-2 act synergistically (see p. 3). However, Eicher does not teach administering VEGF and VEGF-2 at least twice. It would have been obvious to one skilled in the art to repeat the administration of VEGF and VEGF-2 if the first dose were insufficient to induce the formation of new lymphatic vessels. Optimization of conditions through routine experimentation is not considered to be an advancement of the useful arts. MPEP 2144. The skilled artisan would have expected the modified method to be equally effective in inducing the formation of new lymphatic vessels.

Claims 1, 3, 7, 8, 22, 25, 26, 29, 30, 42, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu *et al.* (U.S. Patent No. 6,040,157, submitted by Applicants January 27, 2003). Claims 1, 3, 7, 8, 22, 25, 26, 29, 30, 42, 45, and 46 are as stated above. Hue *et al.* teach methods of administering VEGF-2 polypeptides for treating the loss of lymphatic vessels, occlusions of lymphatic vessels, and lymphangiomas (see column 30, lines 16-20 and column 38, lines 33-36). Hue *et al.* teach VEGF-2 may be used to treat primary lymphedemas such as

Milroy's disease and Lymphedema precox, and secondary lymphedemas (see column 28, line 56 through column 39, line 7). However, Hu *et al.* do not teach administering VEGF-2 at least twice. It would have been obvious to one skilled in the art to repeat the administration of VEGF-2 if the first dose were insufficient to induce the formation of new lymphatic vessels. Optimization of conditions through routine experimentation is not considered to be an advancement of the useful arts. MPEP 2144. The skilled artisan would have expected the modified method to be equally effective in inducing the formation of new lymphatic vessels.

Claims 57-58 and 60-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alitalo *et al.* as discussed above. Claims 57-58 and 60-64 are drawn to methods for inducing formation of new lymphatic vessels by injecting cells or tissues with VEGF-2 or by applying VEGF-2 topically. Alitalo *et al.* teach administering VEGF-2 for inducing the formation of new lymphatic vessels, however Alitalo *et al.* do not teach injecting VEGF-2 or applying it topically. It would have been an obvious variation to one skilled in the art to apply VEGF-2 topically or administer it via injection. One skilled in the art would have been motivated to do so, because these are simply alternate routes of administering medicaments. The skilled artisan would have expected alternate routes to be equally useful in inducing the formation of new lymphatic vessels.

Claims 59, 65, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alitalo *et al.* as discussed above, and further in view of Eicher (WO 99/49882, cited in paper no. 0504). Claims 59, 65, and 81 have the limitation that the VEGF-2 be administered with at least one angiogenic protein. Alitalo *et al.* teach administering VEGF-2, but they do not teach co-administering with an angiogenic protein. Eicher teaches the administration of VEGF and VEGF-2 to promote new blood and lymphatic vessel formation (see p. 4). Eicher teaches that VEGF and VEGF-2 act synergistically (see p. 3). It would have been obvious to one skilled in the art to combine the teachings of Eicher and Alitalo *et al.* One skilled in the art would have been motivated to do so because both references teach administering VEGF-2 for promoting the formation of new lymphatic vessels, and Eicher teaches that VEGF and VEGF-2 act

synergistically, thereby increasing the efficacy of VEGF-2. One skilled in the art would expect the modified method to be as successful if not more successful than that taught by Alitalo *et al.*

Conclusion

NO CLAIMS ARE ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel K. Hunnicutt whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RKH
2/4/05

JANET ANDRES
PRIMARY EXAMINER